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(54) Title: COMPOSITION COMPRISING A TRAMADOL MATERIAL AND A SELECTIVE COX–2 INHIBITOR DRUG

(57) Abstract

This invention relates to a pharmaceutical composition comprising a combination of a tramadol material and a selective COX–2 inhibitor drug and use for treating or preventing pain, inflammation and certain neurological disorders and cancers. The compositions have a synergistic effect, use less of each ingredient and have less opioid side effects such as abuse liability, tolerance, constipation and respiratory depression.

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Composition Comprising a Tramadol Material and a Selective COX-2 Inhibitor Drug

Field of the Invention

The present invention is directed to pharmaceutical compositions useful for treating or preventing pain, inflammation and certain neurological disorders and cancers. More particularly, this invention is directed to pharmaceutical compositions comprising a combination of a tramadol material and a selective cyclooxygenase-2 (COX-2) inhibitor drug.

Background of the Invention

United States Patent No. 3,652,589 discloses a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as tramadol, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of tramadol are found in Arzneim. Forsch. (Drug Res.), 28(I), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that tramadol produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VIth World Congress on Pain, April 1-6 (1990), disclose that tramadol hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that tramadol lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim. Forsch. (Drug Res.), 28(I), 183 (1978)), constipation (I. Arend et al., Arzneim. Forsch. (Drug Res.), 28(I), 199 (1978)), tolerance (L. Flohe et, al., Arzneim. Forsch. (Drug Res.), 28(I), 213 (1978)), and abuse liability (T. Yanagita, Arzneim. Forsch. (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, tramadol may produce certain side effects unique to tramadol including hot flushes and sweating. Despite these side effects, tramadol's combination of non-opioid and opioid activity makes tramadol a very unique drug. Tramadol is currently marketed as an analgesic.

Opioids have for many years been used as analgesics to treat severe pain. They, however, produce undesirable side effects and as a result cannot always be given repeatedly or at high doses. The side effect problems are well documented in the literature. See, for example, T. Reisine and G. Pasternak in "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 9th edition; Hardman et al.; McGraw-Hill, New York, 1996; Chapter 23; pages 521-555 wherein it is disclosed that morphine and its congeners, e.g., codeine, hydrocodone and oxycodone, are opioid agonist analgesics that exhibit side effects such as respiratory depression, constipation, tolerance and abuse liability.

To reduce the side effect problems of opioids, opioids have been combined with other drugs including non-opioid analgesic agents, which lower the amount of opioid needed to produce an equivalent degree of analgesia. It has been claimed that some of these combination products also have the advantage of producing a synergistic analgesic effect. For example, A. Takemori, Annals New York Acad. Sci., 281, 262 (1976) discloses that compositions including combinations of opioid analgesics with drugs other than analgesics exhibit a variety of effects, i.e., subadditive (inhibitory), additive or superadditive. R. Taber et al., J. Pharm. Expt. Thera., 169(1), 29 (1969) disclose that the combination of morphine and methadone, another opioid analgesic, exhibits an additive effect. United States Patent No. 4,571,400 discloses that the combination of dihydrocodeine, an opioid analgesic, and ibuprofen, a non-opioid analgesic, provides superadditive effects when the components are within certain ratios. See also U.S. Patent Nos. 4,587,252 and 4,569,937 which disclose other ibuprofen opioid combinations. A. Pircio et al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and acetaminophen, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.

Combinations of non-opioid analgesics have also been prepared to avoid the side effects associated with opioids, and the combinations are noted to have the benefit of requiring less of each ingredient and producing superadditive effects. G. Stacher et. al., Int. J. Clin. Pharmacol. Biopharmacy, 17, 250 (1979) report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and acetaminophen, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, United States Patent No. 4,260,629 discloses that an orally administered composition of acetaminophen and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals. Furthermore, United States Patent No. 4,132,788 discloses that 5-aroyl-1-(lower)alkylpyrrole-2-acetic acid derivatives, non-opioid analgesics, when combined with acetaminophen or aspirin exhibit superadditive antiarthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic mixtures and of the consumption of a single non-opioid analgesic in large amounts or over long periods (see, D. Woodbury and E. Fingl at page 349). In addition, ibuprofen, aspirin and some other NSAIDs may cause gastrointestinal side effects especially if used repeatedly. See, for example, M.J.S.Langman, Am. J. Med. 84 (Suppl. 2A): 15-19, 1988; P.A. Insel "Goodman and Gilman's, The Pharmacological Basis of Therapeutics", 9th edition; Hardman et al.; McGraw-Hill, New York, 1996; Chapter 27; pages 617-657.

Tramadol has also been combined with other drugs and such compositions have exhibited synergistic effects in treating pain. Specifically, U.S. Patent No. 5,516,803 discloses the combination of tramadol and a non-steroidal anti-inflammatory drug, particularly ibuprofen. U.S. Patent No. 5,468,744 discloses tramadol in combination with any of oxycodone, codeine or hydrocodone and U.S. Patent No. 5,336,691 discloses tramadol in combination with acetaminophen.

Arachidonic acid metabolites such as prostaglandin E_2 (PGE_2), prostaglandin G_2 (PGG_2), prostaglandin H_2 (PGH_2), prostaglandin I_2 (PGI_2) and thromboxane B_2 (TXB_2) play major roles in the inflammation process. Compounds that are highly selective inhibitors of COX-2 and, thus, prevent prostaglandin production, have been identified (Vane et al., Ann. Rev. Pharmacol. Toxicol. 38, 97 (1998)). Furthermore, it has been determined that such compounds, while inhibiting the COX-2 enzyme, possess analgesic and antiinflammatory action (Seibert et al., Proc. Natl. Acad. Sci, USA, 91(12) 12013 (1994).

United States Patent 5,994,381 discloses a group of heteroaromatic oxazole compounds as highly effective selective COX-2 inhibitor drugs, in particular, the compound JTE-522 (5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole).

A pharmaceutical composition comprising an opioid analgesic together with a COX-2 inhibitor drug has been described in *WO* 99/13799. Listed as an opioid analgesic, tramadol was claimed for use in the described pharmaceutical composition. However, only pharmaceutical compositions comprising a combination of morphine:nabumetone in a 1:1000 ratio based on their respective ED_{50} values and a combination of morphine:meloxicam in a 1:10 ratio were disclosed as synergistic analgesic combinations.

Combinations of a nontoxic N-methyl-D-aspartate receptor antagonist, a COX-2 inhibitor drug and other pharmaceutically active substances were described as analgesic potentiators in *WO* 98/50075. Further, non-narcotic and narcotic analgesics were claimed as pharmaceutically active substances. Listed as a non-narcotic analgesic, tramadol was claimed for use in the described combination. However, only acetaminophen, aspirin and ibuprofen were disclosed as non-narcotic analgesic potentiators.

Therefore, no reference has heretofore disclosed pharmaceutical compositions comprising combinations of the centrally acting analgesic tramadol and a selective COX-2 inhibitor drug and demonstrated that such compositions have a synergistic effect while using less of each ingredient. More particularly, pharmaceutical compositions comprising a combination of tramadol hydrochloride and the selective COX-2 inhibitor compound 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole have not been previously described.

Therefore, it is an object of the present invention to produce a combination product with a tramadol material having improved properties. It is also an object of the present invention to produce a combination product with a tramadol material and a selective COX-2 inhibitor drug wherein an instant pharmaceutical composition has a synergistic effect while using less of each ingredient. It is another object of the present invention to produce a combination product with tramadol hydrochloride and the selective COX-2 inhibitor drug 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole, wherein the pharmaceutical compositions have a synergistic effect, use less of each ingredient and, thus, reduce the number and severity of side effects associated with each agent. A further object of the present invention is to provide a method for treating or preventing pain, inflammation and certain neurological disorders and cancers in mammals.

Disclosure of the Invention

Briefly, according to the present invention, there is provided a pharmaceutical composition comprising a combination of a tramadol material and a selective COX-2 inhibitor drug, wherein the tramadol material and the selective COX-2 inhibitor drug are present in a ratio based on a fraction of their respective 50% effective dose (ED_{50}) values, which ratio is from about 1:1 to about 1:300 or from about 1:1 to about 300:1.

The present invention further provides a method for treating or preventing pain, inflammation and certain neurological disorders and cancers in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition for treating or preventing pain, inflammation and certain neurological disorders and cancers comprising a combination of a tramadol material and a selective COX-2 inhibitor drug, wherein the tramadol material and the selective COX-2 inhibitor drug are present in a ratio based on a fraction of their respective ED_{50} values, which ratio is from about 1:1 to about 1:300 or from about 1:1 to about 300:1.

Further, a pharmaceutical composition according to this invention is useful for treating or preventing pain and inflammation including but not limited to osteoarthritis or rheumatoid arthritis and certain neurological disorders and cancers including but not limited to Alzheimer's disease, colorectal cancer or colon polyps.

Detailed Description of the Invention

The present invention is generally directed to pharmaceutical compositions comprising a tramadol material and a selective COX-2 inhibitor drug. The tramadol material is any one of (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol (tramadol), its N-oxide derivative ("tramadol N-oxide"), and its O-desmethyl derivative ("O-desmethyl tramadol") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the tramadol material. Tramadol is commercially available from Grunenthal or may be made by the process described in United States Patent No. 3,652,589, which is herein incorporated by reference.

Tramadol N-oxide is prepared by treating tramadol as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g.,

methanol or isopropanol, with, but preferably without heating. See, "Reagents For Organic Synthesis", 1, 471, Fieser & Fieser eds., Wiley N.Y; (1987), B. Kelentey et al., Arzneim. Forsch., 7, 594 (1957). With heating, the reaction takes about 1 hour, whereas without heating the reaction takes about 3 days. Following the oxidation, the mixture is treated with an agent, e.g. PtO_2 or preferably Pt/C, for about a day, to destroy the excess hydrogen peroxide. The mixture is filtered, followed by the evaporation of the filtrate and then the residue is recrystalized from an organic solvent mixture, e.g., methylene chloride/ethyl acetate.

O-desmethyl tramadol is prepared by treating tramadol as a free base under O-demethylating reaction conditions, e.g., reacting it with a strong base such as NaOH or KOH, thiophenol and diethylene glycol (DEG) with heating to reflux. See, Wildes et al., J. Org. Chem., 36, 721 (1971). The reaction takes about an hour, followed by cooling and then quenching in water of the reaction mixture. The quenched mixture is acidified, extracted with an organic solvent such as ethyl ether, basified and then extracted with a halogenated organic solvent such as methylene chloride. The extract is then dried and the solvent evaporated to yield the O-desmethyl product, which may then be short-path distilled, converted to its corresponding salt, e.g., treated with an acidified (HCl/ethanol) solution, and recrystallized from an organic solvent mixture, e.g., ethanol/ethyl ether.

Selective COX-2 inhibitor drugs according to the present invention are analgesic and antiinflammatory agents known to be selective COX-2 inhibitor drugs. The most relevant assay for the determination of selectivity is considered to be inhibition of the action of the recombinant human COX-1 and COX-2 enzymes. Alternatively, one may use the enzymes present in human blood (JR Vane et als, Ann Rev Pharmacol Tox 38:97-120, 1998).

Selective COX-2 inhibitor drugs according to the present invention are those compounds whose action in inhibiting the COX-2 enzyme are at least

10-fold to 100-fold more potent for inhibiting the COX-2 enzyme than for inhibiting the COX-1 enzyme. Examples of compounds known to be highly selective inhibitors of the COX-2 enzyme are: Celebrex® celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide), Vioxx® rofecoxib (4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone), JTE-522 (5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole) and the difluoro analog to JTE-522 (5-(4-aminosulfonyl-3,5-difluorophenyl)-4-cyclohexyl-2-methyloxazole). Such compounds are known to be effective for treating or preventing pain, inflammation and certain neurological disorders and cancers.

In pharmaceutical compositions of the present invention, the selective COX-2 inhibitor drug portion of the compositions may either be a single selective COX-2 inhibitor drug or a combination of one or more selective COX-2 inhibitor drugs. Accordingly, as used herein, pharmaceutical compositions comprising a tramadol material and a selective COX-2 inhibitor drug include all of these possibilities. It is intended that pharmaceutical compositions comprising the combination of a tramadol material and a selective COX-2 inhibitor drug as the active ingredients in synergistic ratios based on a fraction of their respective ED_{50} values as well as methods of preparing the instant compositions in synergistic ratios are also encompassed within the present invention.

According to compositions of the present invention, a tramadol material and a selective COX-2 inhibitor drug are present in a ratio based on a fraction of their respective ED_{50} values which ratio may vary from about 1:1 to about 1:300 or, reversibly, from about 1:1 to about 300:1, depending upon the desired result. Preferably, compositions of the invention contain a majority of a tramadol material.

Compositions comprising a combination of a tramadol material and a selective COX-2 inhibitor drug within these ratios exhibit synergistic effects.

Pharmaceutical compositions according to the present invention comprise an effective amount of a tramadol material in combination with a selective COX-2 inhibitor drug for treating or preventing pain, inflammation and certain neurological disorders and cancers in a mammal in need thereof. Preferably, instant compositions comprise a combination of tramadol hydrochloride with 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole.

Pharmaceutical compositions comprising a tramadol material and a selective COX-2 inhibitor drug as the active ingredients in an intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The compositions may also be administered by means of an aerosol. In preparing the compositions in an oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations (such as suspensions, elixirs and solution), water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. In the case of oral solid preparations (such as, for example, powders, capsules and tablets), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, may be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. In the case wherein one or more other pharmaceutically active components are added to compositions combining a tramadol material and a selective COX-2 inhibitor drug, those components may be added in amounts known in the art and may be given at dosages

conventional for such components. The pharmaceutical compositions of the present invention will generally be in the form of a dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, wherein the preferred amount of each of the active ingredient to be contained therein is determined by the aforementioned ratios.

The dosage unit is calculated based on the amount of active ingredient which may be given to a 70 kg human subject in a single dose. The instant pharmaceutical compositions may be given at a daily dose of from about 0.1 mg/day to about 800 mg/day of the active ingredients and, preferably from about 0.3 to 200 mg/day of the active ingredients. However, it will be appreciated that the precise dose of the active ingredients will vary depending upon the relative amount of each active component being used, upon the particular tramadol material and selective COX-2 inhibitor drug being used and upon the aforementioned ratios. Thus, for example, a formulation demonstrating synergistic activity may contain from about 0.6 mg to about 60 mg of a tramadol material and from about 2 mg to about 20 mg of a selective COX-2 inhibitor drug such as 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole. Also, the tramadol material and a selective COX-2 inhibitor drug need not be present in the same formulation to achieve the results described herein. They may be administered individually at about the same time or in a single tablet.

The pharmaceutical compositions of the present invention are useful for treating or preventing pain, inflammation and certain neurological disorders and cancers in mammals by the administration of compositions comprising a combination of a tramadol material and a selective COX-2 inhibitor drug. Those skilled in the art of treating mammalian pain know that the types of pain experienced by mammals are varied. Examples of mammalian pain include, but are not limited to, centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain and neuropathic pain states, all of which would include acute pain such as

caused by acute injury, trauma or surgery; chronic pain such as caused by neuropathic conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes or cluster or migraine headaches. Examples of inflammation include, but are not limited to, those caused by osteoarthritis, rheumatoid arthritis or as sequela to disease, acute injury or trauma. The instant compositions are also useful for treating or preventing certain neurological disorders including, but not limited to, degeneration of nervous system cells due to Alzheimer's disease and certain cancers including, but not limited to, colorectal cancer and colon polyps.

Pharmaceutical compositions comprising a combination of a tramadol material and a selective cyclooxygenase-2 (COX-2) inhibitor drug can be evaluated for efficacy by use of one or more of the following tests. As appreciated by those skilled in the art, the following experimental examples describe the invention in greater particularity and are intended to be a way of illustrating but not limiting the invention. Further, the efficacy of pharmaceutical compositions of the present invention may be determined by statistical comparison of results achieved in the presence of an instant pharmaceutical composition to that which is achieved in its absence. Alternatives may also be utilized.

Example 1

Preparation of Composition Doses of Tramadol and a Selective COX-2 Inhibitor Drug

The preparation of different ratios of compositions comprising a combination of a tramadol material and a selective COX-2 inhibitor drug such as 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole are effected by preparing solutions having concentrations or suspensions expressed in mg of active drug per 10 mL of distilled water or in mg of active drug per suspension of 10 mL of 0.5% hydroxypropyl methylcellulose in distilled water. For example, 40 mg of a tramadol material such as tramadol hydrochloride as the free base is added to a 10 mL suspension of 0.5% hydroxypropyl

methylcellulose in distilled water. Then the appropriate volume of the tramadol hydrochloride solution (in this case, 40 mg/10 mL) is added to the appropriate neat amount of the selective COX-2 inhibitor drug 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole, yielding a 10mL suspension of a 1:1 ratio based on a fraction of the respective ED_{50} values of tramadol hydrochloride: 5-(4-aminosulfonyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (40 mg:40 mg). The range of doses for each ratio tested are prepared separately in a similar manner. Accordingly, other ratios of pharmaceutical compositions comprising a combination of a tramadol material and a selective COX-2 inhibitor drug may also be similarly prepared at various concentrations.

Example 2

Mouse Abdominal Irritant Test

The procedure used in detecting and comparing the analgesic activity of different classes of analgesic drugs for which there is a good correlation with human efficacy is the prevention of acetylcholine-induced abdominal constriction in mice (H. Collier, et al., Br. J. Pharmacol., 1968, 32, 295).

Animals

Male CD1 mice (weighing from 18-24 g) are utilized in determining the analgesic effects associated with the compositions of the invention.

Animal Dosing

The mice are all dosed orally with compositions comprising a combination of tramadol hydrochloride (calculated as the base) and the selective COX-2 inhibitor drug (calculated as the base) or compositions of each agent, separately dissolved in distilled water or dissolved in a suspension of 0.5% hydroxypropyl methylcellulose in distilled water. The dosing volume is 2 mL/kg.

Analgesic Effect

The mice are then injected intraperitoneally with a challenge dose of acetylcholine bromide. The acetylcholine is completely dissolved in distilled water at a concentration of 5.5 mg/kg and injected at the rate of 0.20 mL/20 g. For scoring purposes, an "abdominal constriction" is defined as a contraction of the abdominal musculature accompanied by arching of the back and extension of the limbs. The mice are observed for 10 minutes for the presence or absence of the abdominal constriction response beginning immediately after receiving the acetylcholine dose, administered at a certain time after the oral administration of tramadol hydrochloride alone, a selective COX-2 inhibitor drug alone, combined doses of tramadol hydrochloride and a selective COX-2 inhibitor drug or vehicle. Each mouse is used only once.

Example 3

Rat Abdominal Irritant Test

The procedure used in detecting and comparing the analgesic activity of different classes of analgesic drugs for which there is a good correlation with human efficacy is the prevention of acetylcholine-induced abdominal constriction in rats (Von Voigtlander and Lewis, Drug Dev. Res., 2:577, 1982),

Animals

Male, Sprague-Dawley rats (Charles River Laboratories), weighing 80-120 g, were housed 5-10 per container in a climate-controlled, virus free environment for at least 5 days prior to testing. Food and water were available *ad libitum* up to test time. The animals were individually weighed and allowed to acclimate to conditions before testing.

Animal Dosing

Test drug was dissolved in sterile water (vehicle) and orally administered in a volume of 2 mL/kg.

Analgesic Effect

The rat air-induced abdominal irritant test used herein was performed as described by Von Voigtlander, et al., with minor modification. Other irritant sources may be used by one skilled in the art. Thirty minutes after p.o. administration of 2 mL/kg of test drug, the animals were given i.p. injections of 10 mL of air. Each rat was placed into a plastic observation box and was observed for a maximum of 30 minutes for the occurrence of an abdominal irritant response (as defined under the mouse acetylcholine-induced abdominal irritant test). The percent of inhibition of this response was calculated as follows:

% Inhibition =

100 x (Number of Nonresponders)/Number of Animals in Group)

The antinociceptive activity of rofecoxib and celecoxib were evaluated in the rat abdominal irritant test one hour following oral administration of each drug. At the doses tested (rofecoxib at 30 mg/kg; celecoxib at 10, 30, 60 and 100 mg/kg) neither compound exhibited antinociceptive activity.

Example 4

Carrageenan Paw Hyperalgesia Test

The procedure used in detecting and comparing the antiinflammatory activity of different classes of antiinflammatory drugs for which there is a good correlation with human efficacy is the carrageenan paw hyperalgesia test (Dirig, et al., J. Pharmacol Expt Therap. 1998, **285**, 1031).

Animals

Male, Sprague-Dawley rats (Charles River Laboratories) are housed in a climate-controlled, virus free environment for at least 5 days prior to testing. Food and water are available *ad libitum* up to test time.

Animal Dosing

Test rats are immunized by injecting an irritant (e.g., 0.1 ml of a 0.3-1.0% carrageenan solution in 0.9% saline) subcutaneously into the subplantar tissue of one of the hind paws to stimulate an acute inflammatory reaction. Control rats receive a similar saline injection.

The rats are all dosed orally with compositions comprising a combination of tramadol hydrochloride (calculated as the base) and the selective COX-2 inhibitor drug (calculated as the base) or each agent separately, dissolved in either distilled water or dissolved in a suspension of 0.5% hydroxypropyl methylcellulose in distilled water at a fixed time following carrageenan injection. The dosing volume is 2 mL/kg. The hyperalgesic response of the animal is subsequently evaluated at a fixed later time.

Measurement of Hyperalgesia

Hyperalgesia is assessed by measurement of a response to a thermal or a mechanical stimulus. Measurement of thermal hyperalgesia is made with a standard laboratory hot plate apparatus, whose surface temperature is precisely determined and evenly maintained. Alternatively, hyperalgesia is evaluated with a commercially available Hargreaves apparatus which selectively elevates the temperature of an individual paw (Dirig, et al., J Neurosci Methods, 1997, **76**, 183). With either apparatus, hyperalgesia is measured as a reduced latency to response compared to the latency of an untreated or vehicle treated animal, and the analgesic effect of the test compound is seen as a (partial) restoration of the latency toward normal (Dirig, et al., J Pharmcol Expt Therap, 1998, **285**, 1031). A response is defined as any shaking, licking, or tucking of the treated paw.

Assessment of hyperalgesia by a mechanical means is effected with a device designed to apply a precisely calibrated force to the paw. Hyperalgesia is measured as reduction in the force, measured in grams, needed to elicit paw withdrawal or vocalization (Randall and Selitto, Arch Int Pharmacodyn, 1957, **4**,

409). The analgesic effect of the test compound is seen as a (partial) restoration of the force eliciting a response toward normal.

Example 5

Analysis of Synergistic Effect

The synergistic interaction between a tramadol material and a selective COX-2 inhibitor drug is determined at precise dosage ratios of tramadol hydrochloride and selective COX-2 inhibitor drugs. Multiple (typically 4-6) coded doses of each selected combination are studied for effectiveness using an experimental design which permits the complete randomization of the separate dosage forms tested.

Analysis

The analysis of possible synergistic effect for compositions at each fixed ratio is determined as disclosed by R. J. Tallarida, et al., Life Sci., 1989, 45, 947. This procedure involves the determination of the total amount in the mixture that is required to produce a specified synergistic antiallodynic effect at the 50% dose level (that is, the ED_{50mix} or Z_{mix}) and the corresponding total amount that would be expected under simple additivity (ED_{50add} or Z_{add}). Where it is established that $Z_{mix} < Z_{add}$ for a specific fixed-ratio, then that composition has a synergistic antiallodynic effect. Both the quantities ED_{50mix} and ED_{50add} are random variables. ED_{50mix} is determined from the dose-response curve for a specific fixed-ratio of the components; ED_{50add} is calculated from the ED_{50} values for the individual drugs. Z_{mix} is then compared to Z_{add} via a Student's t-test.

WE CLAIM:

1. A pharmaceutical composition comprising a combination of a tramadol material and a selective COX-2 inhibitor drug, wherein the tramadol material and the selective COX-2 inhibitor drug are present in a ratio based on a fraction of their respective ED_{50} values, which ratio is from about 1:1 to about 1:300 or from about 1:1 to about 300:1.

2. The pharmaceutical composition of claim 1, wherein the ratio based on a fraction of the ED_{50} value for each component is a ratio from about 1:1 to about 1:30 and from about 1:1 to about 30:1.

3. The pharmaceutical composition of claim 1 wherein the tramadol material is tramadol hydrochloride.

4. The pharmaceutical composition of claim 3 wherein the tramadol hydrochloride is racemic.

5. The pharmaceutical composition of claim 3 wherein the tramadol hydrochloride is an enantiomer.

6. The pharmaceutical composition of claim 1 wherein the fraction of the ED_{50} value for tramadol hydrochloride is from about 0.0001 to about 0.75.

7. The pharmaceutical composition of claim 1 wherein the fraction of the ED_{50} value for tramadol hydrochloride is from about 0.001 to about 0.05.

8. The pharmaceutical composition of claim 1 wherein the fraction of the ED_{50} value for tramadol hydrochloride is from about 0.0015 to about 0.025.

9. The pharmaceutical composition of claim 1 wherein the fraction of the ED_{50} value for tramadol hydrochloride is from about 0.0025 to about 0.01.

10. The pharmaceutical composition of claim 1 wherein the fraction of the ED_{50} value for tramadol hydrochloride is from about 0.005 to about 0.0075.

11. The pharmaceutical composition of claim 1, wherein the selective COX-2 inhibitor drug is at least one member selected from the group consisting of celecoxib, rofecoxib, valdecopxib, parecoxib, JTE-522, the difluoro analog to JTE-522, salts thereof, complexes thereof and mixtures of any of the foregoing.

12. The pharmaceutical composition of claim 1 wherein the selective COX-2 inhibitor drug is a combination of two or more selective COX-2 inhibitor drugs.

13. The pharmaceutical composition of claim 1 wherein the selective COX-2 inhibitor drug is a single COX-2 inhibitor drug.

14. The pharmaceutical composition of claim 1 wherein the selective COX-2 inhibitor drug is JTE-522.

15. The pharmaceutical composition of claim 1 further comprising a pharmaceutically acceptable carrier.

16. A method for treating or preventing a pharmacological condition in a mammal in need thereof comprising administrating to the mammal a therapeutically effective amount of the pharmaceutical composition of claim 1.

17. The method of claim 16 wherein the therapeutically effective amount of the pharmaceutical composition is from about 0.1 mg/day to about 800 mg/day.

18. The method of claim 16 wherein the therapeutically effective amount of the pharmaceutical composition is from about 0.3 mg/day to about 200 mg/day.

19. The method of claim 16 wherein the tramadol material and the selective COX-2 inhibitor drug are administered individually at about the same time.

20. The method of Claim 16 wherein the tramadol material and the selective COX-2 inhibitor drug are administered in a single tablet.

21. The method of claim 16 wherein the tramadol material is tramadol hydrochloride and the selective COX-2 inhibitor drug is JTE-522.

22. The method of claim 16 wherein the pharmacological condition is selected from pain, inflammation, neurological disorder or cancer.

23. The method of claim 16 wherein pain is selected from centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, progressive disease related pain, neuropathic pain, acute pain caused by acute injury, trauma or surgery, chronic pain caused by neuropathic conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes, cluster headaches or migraine headaches.

24. The method of claim 16 wherein inflammation is selected from osteoarthritis, rheumatoid arthritis or as sequela to disease, acute injury or trauma.

25. The method of claim 16 wherein the neurological disorder is Alzheimer's disease.

26. The method of claim 16 wherein cancer is selected from colorectal cancer or colon polyps.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 00/05119

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P19/10 A61P19/02 A61P35/00 A61P29/00 A61P25/02
A61P25/28 A61P25/04 A61P25/06 A61K45/06 A61K31/42
A61K31/415 A61K31/365 //(A61K45/06,31:135),(A61K31/42,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 29022 A (ALGOS PHARM CORP) 25 May 2000 (2000-05-25) the whole document —	1-26
P,X	WO 99 13799 A (EURO CELTIQUE SA) 25 March 1999 (1999-03-25) cited in the application page 5, line 7-10 page 6, line 23-27 page 7, line 9 -page 8, line 27 page 10-11; table 1 page 13, line 21 -page 15, line 15 page 18; claims 1,5,10 page 19, line 15-21 page 22 — -/—	1,2,11, 13, 15-20, 22-24

[X] Further documents are listed in the continuation of box C.

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° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2000	04/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kanbier, D

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 00/05119

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 31:135),(A61K31/415,31:135),(A61K31/365,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 546 676 A (MCNEILAB INC) 16 June 1993 (1993-06-16) cited in the application page 3, line 11-49; claims 1-5,8-15 page 4, line 6-11 page 4, line 19-30 page 4, line 42-46 — -/—	1-5,13, 15-20, 22,23

[X] Further documents are listed in the continuation of box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kanbier, D

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 00/05119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 06708 A (SEARLE & CO) 19 February 1998 (1998-02-19)	1,2,4-6, 13, 15-18, 20,22-26
A	page 1, line 6-12; claims 6- page 2, line 10-12 page 12, line 8 -page 13, line 27 page 14, line 34 -page 15, line 14 page 15, line 20-27 page 16, line 17-21	6-10,14, 17-21
X	WO 98 50075 A (ALGOS PHARM CORP) 12 November 1998 (1998-11-12) cited in the application	1,13,15, 16,19, 20,22
A	page 2, line 4-7 page 5, line 9 -page 7, line 24 page 11, line 24 -page 12, line 8 page 14, line 17-23	11
X	WO 98 17268 A (ALGOS PHARM CORP) 30 April 1998 (1998-04-30) page 1, paragraph 2; claims 1,8,9 page 12, paragraph 2 page 10-11	1,13, 15-17, 20,22,23
A	US 5 994 381 A (MATSUSHITA MUTSUYOSHI ET AL) 30 November 1999 (1999-11-30) cited in the application examples 2,,2	14,21
A	MOROZ ET AL: "Use of Tramadol HCl in Therapeutic Operative Dentistry: Clinical Investigation" CURRENT THERAPEUTIC RESEARCH, vol. 4, no. 3, March 1991 (1991-03), pages 371-375, XP000921286 page 372	1-26

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10, 12, 13, 15-20 and 22-26 relate to compositions and methods defined inter alia by reference to a desirable characteristic or property, namely selective inhibition of cyclooxygenase 2 (COX-2). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the complete claimed scope is impossible.
Independent of the above reasoning, these claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action and/or pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 1, 2, 11-20 and 22-26 relate to an extremely large number of possible compounds within the claimed compositions by way of the term "tramadol material".
In fact, due to this terminology, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises which renders a complete search of these claims impossible.

Present claims 1-26 also relate to a composition and methods defined (inter alia) by reference to the following parameter(s):
"ratio based on a fraction of ... ED50 values" and
"a fraction of ... ED50 value"
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. These parameters are not clear from the claims, nor are they explained sufficiently in the description and/or examples to enable a meaningful search for them. It is therefore impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Moreover, even if the meaning of the "ratio" above were clear, its claimed interval (1:1-1:300 OR 1:1-300:1) is such as to pose no clear or distinguishable restriction on the subject matter of independent claims 1 and 16, i.e. combinations of tramadol and COX-2 inhibitors and their use. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compositions and methods involving tramadol HCl (enantiomeric/racemic) and the COX-2 inhibitors specifically mentioned in claims 11, 14 and 21, with due regard to the decription and the general idea underlying the application.

Therefore all claims (including claim 21) were searched INcompletely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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Int. ational Application No
PCT/US 00/05119

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